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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/787,559	06/18/2001	Michael Kramer	113.1010	3025

41288 7590 01/05/2006

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EXAMINER	
ANGELL, JON E	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 01/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/787,559	KRAMER ET AL.	
	Examiner	Art Unit	
	Jon Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-6,8-11,17,18,20 and 24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-6,8-11,17,18,20 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 March 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/20/05 has been entered.

The amendment filed 9/20/05 is acknowledged. The amendment has been entered. Claims 2-6, 8-11, 17, 18, 20 and 24a re currently pending in the application and are addressed herein.

Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Claim Objections

Applicant is advised that should claim 3 be found allowable, claim 4 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). In the instant case, claims 3 and 4 are identical.

Claim 5 is objected to because it appears to be grammatically incorrect. Specifically the phrase, "stringent hybridization conditions with to the nucleotide sequence" is incorrect. It appears that Applicants merely forgot to delete the word "with" from the claim.

Claim 18 is objected to because it appears to be grammatically incorrect. Specifically the phrase, "A method Method for the diagnostic..." is incorrect. It appears that Applicants merely forgot to delete the second "Method" from the claim.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 2-6, 8-11, 17, 18, 20 and 24 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant claims are drawn to an isolated nucleic acid encoding a protein that is functionally identical to a protein that occurs naturally in human keratinocytes wherein the protein has the sequence of SEQ ID NO: 1 or SEQ ID NO: 4, as well as: (1) as partial sequences of SEQ ID NO: 1 or SEQ ID NO: 4 wherein the partial sequences are more than 8 nucleotides, (2) a nucleotide sequence that hybridizes to at least about 8 nucleotides under conventional stringent conditions to SEQ ID NO: 1 or SEQ ID NO: 4 or hybridizes completely with SEQ ID NO: 1 or SEQ ID NO: 4 under low stringency conditions. Therefore, the limitation of the claims

create genus situations where the number of nucleic acids potentially comprises millions or more different species of nucleic acids encoding proteins functionally identical to pKe#122. For example, in a minimal way, Applicant has only disclosed the protein named pKe#122, which is encoded by SEQ ID No. 1 or SEQ ID No. 4. As written, the claims encompass nucleic acids that encode a protein that is functionally identical to pKe#122 and includes variants, derivatives and fragments of the disclosed sequences.

Furthermore, a close analysis of the claims reveals that the phrase "or a nucleotide sequence that hybridizes to at least about 8 nucleotides under conventional stringent conditions with one of the claimed sequences" indicates that the claims encompass nucleic acid sequences which merely hybridize to a nucleic acid sequences encoding a protein that is functionally identical to pKe#122. As such, the claims encompass nucleic acid sequences which hybridize to the sequences encoding the functionally identical protein, but which may not actually encode a functionally identical protein. Therefore, the claims encompass a genus of molecules that possibly comprises millions of different molecules. Applicant has express possession of only two nucleic acid species that encode the functionally active protein (SEQ ID No. 1 and SEQ ID No. 4) in a genus which comprises possibly millions of different species.

The written description guidelines note regarding such genus/species situations that "Satisfactory disclosure of a 'representative number' depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for written description.) Here, no common elements or attributes of the sequences that are critical to any functionally identical molecule are disclosed. Additionally, the elements or attributes not critical for to any functionally identical molecules are not disclosed. Further, there is not any methodology presented to determine such common elements or attributes.

With regard to the written description, all of the claims encompass sequences different from those disclosed in the specific SEQ ID Nos. which include modifications permitted by the "functionally identical" language for which no written description is provided in the specification.

> It is noted that in Fiers v. Sugano (25 USPQ2d, 1601), the Fed. Cir. concluded that "...if inventor is unable to envision detailed chemical structure of DNA sequence coding for specific protein, as well as method of obtaining it, then conception is not achieved until reduction to practice has occurred, that is, until after gene has been isolated...conception of any chemical substance, requires definition of that substance other than by its functional utility."

In the instant application, only the sequences of the disclosed SEQ ID Nos. are described. Also, in Vas-Cath Inc. v. Mahurkar (19 USPQ2d 1111, CAFC 1991), it was concluded that:

> "...applicant must also convey, with reasonable clarity to those skilled in art, that applicant, as of filing date sought, was in possession of invention, with invention being, for purposes of "written description" inquiry, whatever is presently claimed."

In the application at the time of filing, there is no record or description which would demonstrate conception or written description of any nucleic acids encoding molecules functionally identical to pKe#122 other than SEQ ID NO:1 and SEQ ID NO:4.

Claim 18 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include

> (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The instant claim is drawn to use of a sense or antisense oligonucleotide for the diagnostic and/or therapeutic treatment of dermatological diseases or for the cosmetic treatment in particular of the epidermis. Therefore the nature of the invention encompasses gene therapy, including antisense oligonucleotide therapy.

The breadth of the claims

The breadth of the claim is very broad. For instance, the claim encompasses a DNA or RNA oligonucleotide that is useful for the diagnosis and/or treatment of any dermatological disorder or that is useful for any cosmetic treatment in any species of animal.

The unpredictability of the art and the state of the prior art

At the time of filing the relevant prior art regarded gene therapy and antisense oligonucleotide gene therapy as highly unpredictable. With regard to oligonucleotides as therapeutic reagents, the bulk of the art indicates the difficulty in utilization of antisense therapies. Probst et al. (TIGs Vol. 12(8):290-291; 1996) notes,

> "The mechanism of antisense oligonucleotide action is poorly understood and relies primarily on speculation and, as recently described in Nature Medicine and Science, seems to have 'growing pains' due to the lack of knowledge regarding antisense action. Improper use of molecular terminology (ref omitted) will also lead to misunderstandings,

> as will incompletely analyzed cellular and molecular effects evoked by antisense oligonucleotides (page 90, column 1, third paragraph)".

Regarding gene delivery in vivo, Harris et al. (TIGs Vol. 12(10):400-405; 1996) stated that,

> "The major hurdle now is the poor efficiency of gene delivery in vivo with the gene transfer technology presently available, but we anticipate that this will be overcome by further modifications of viral vectors and the development of synthetic systems combining the best elements of a variety of vectors (page 405)".

The prior art also supports the unpredictable nature of the art. It is unpredictable which formulations, compounds and delivery modes will function in an in vivo setting. This unpredictability is evidenced in a report in Science (Vol. 269:1050-1055) which states that, "So far, there has been no unambiguous evidence that genetic treatment has produced therapeutic benefit (page 1050, column 1)".

There appears to be no prior art on the nucleic acid molecules encoding pKe#122, the pKe#122 protein itself, or on the function of the pKe#122 protein. There is no recognition in the prior art that pKe#122 is involved in any way in any dermatological disorder. Furthermore, there is no evidence in the prior art that oligonucleotides which hybridize to SEQ ID No. 1 or SEQ ID No. 4 would be useful in diagnosing or treating any dermatological disorder or that the oligonucleotides would be useful for cosmetic treatment as the protein encoded by SEQ ID No. 1 and SEQ ID No. 4 (pKe#122) had not been associated with any dermatological disorder.

Working Examples and Guidance in the Specification

The specification has only one working examples, of oligonucleotides that hybridize to SEQ ID No. 1 or SEQ ID No. 7. The working example (Example 6 in the instant specification) is an experiment where cells were treated in vitro with antisense oligonucleotides. The treated

cells displayed an altered morphology which allowed the applicants to conclude that "cells treated with pKe#122-specific antisense-oligonucleotides show an increased tendency toward differentiation (see page 20, first paragraph)." However, there are no working examples of in vivo use of the antisense oligonucleotides, the results of which are critical to determining the therapeutic effectiveness of the reagents. There are also no examples demonstrating the accuracy of the oligonucleotides in diagnosing any disease/disorder. There are no working examples or guidance in the specification on methods of using the oligonucleotides for cosmetic treatment. Therefore, it is unpredictable that the oligonucleotides could successfully be used to diagnose and/or treat any dermatological disorder, or that the oligonucleotide could be successfully used in cosmetic treatment.

Quantity of Experimentation

The quantity of experimentation required is extremely large since pKe#122 (the protein encoded by SEQ ID No. 1 and SEQ ID No. 4) has not been associated with any dermatological disorder. Therefore, it must first be determined if pKe#122 is associated with a dermatological disorder. If pKe#122 is not associated with any dermatological disorder, then the oligonucleotides would not be useful in diagnosing and/or treating any dermatological disorder. Determining if pKe#122 is involved in dermatological disorders would require testing for the alteration of pKe#122 in every possible dermatological disorder. The alterations could include overexpression, loss of expression, or mutations that increase or decrease the activity of pKe#122. Once it was determined that pKe#122 was associated with a dermatological disorder, the efficacy of the oligonucleotide in treating the disorder would have to be tested, a process that includes in vitro experiments, testing in animals, and finally clinical studies in human subjects.

This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of the skill in the art

The level of the skill in the art is deemed to be high.

Conclusion

Considering the high degree of unpredictability of gene therapy recognized in the art, the breadth of the claims, the lack of working examples and guidance in the specification; and the high degree of skill required, it is concluded that the amount of experimentation required to perform the broadly claimed method is undue.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 2, 3, 4 and 17 are rejected under 35 U.S.C. 102(b) based upon a public use or sale of the invention.

Claim 2 encompasses partial sequences of SEQ ID NO: 1 or SEQ ID NO: 4 wherein the partial sequences are more than 8 nucleotides, as well as a nucleotide sequence that hybridizes to at least about nucleotides under conventional stringent conditions to SEQ ID NO: 1 or SEQ ID NO: 4. It is noted that the phrase "a nucleotide sequence that hybridizes to at least about

nucleotides under conventional stringent conditions to SEQ ID NO: 1 or SEQ ID NO: 4" does not limit the claims to oligonucleotides that are 8 or more nucleotides in length. As such, an oligonucleotide that is 6 nucleotides long (i.e., a hexanucleotide) and which is 100% identicial to 6 nucleotides of SEQ ID NO: 1 or SEQ ID NO: 4 would be encompassed by the claims as it would hybridize to "at least about 8 nucleotides" of SEQ ID NO: 1 or SEQ ID NO: 4 under conventional stringent conditions. Claims 3 and 4 are drawn to the isolated nucleic acid of claim 2 wherein the nucleic acid is obtained from a natural, synthetic or half-synthetic source. Claim 17 encompasses a reagent that is at least one nucleic acid according to claim 2.

Random hexanucleotides (6mers) were available for sale as early as 1997 (see 1997 Boehringer Mannheim Catalog, page 95). The hexanucleotide mix available comprised, "mixture of hexamer nucleotides of all possible sequences for random primed DNA labeling." Therefore, there existed within the hexanucleotide mix at least one nucleotide sequence that would be 100% identical one of the sequences encompassed by the claims which would necessarily hybridize wholly or in part with the target sequence under the claimed conditions. Claim 3 encompass the nucleotide sequence of claim 2 that is obtained from natural, synthetic or half-synthetic source. The hexamers for sale by Boehringer were synthetically synthesized.

5. Claims 2, 3, 4 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Mierendorf et al. (U.S. patent 5,629,179).

As mentioned above, Claim 2 encompasses partial sequences of SEQ ID NO: 1 or SEQ ID NO: 4 wherein the partial sequences are more than 8 nucleotides, as well as a nucleotide sequence that hybridizes to at least about nucleotides under conventional stringent conditions to

SEQ ID NO: 1 or SEQ ID NO: 4. Claims 3 and 4 are drawn to the isolated nucleic acid of claim 2 wherein the nucleic acid is obtained from a natural, synthetic or half-synthetic source. Claim 17 encompasses a reagent that is at least one nucleic acid according to claim 2.

Mierendorf et al. teaches a method and kit for making a cDNA library wherein the kit comprises random octamer oligonucleotides (i.e. nucleic acids that are 8 nucleotides in length) over every possible sequence (see column 7, line 59-column 8, line 6). Mierendorf et al. teaches a kit comprising every possible octamer oligonucleotide. Therefore, the kit taught by Mierendorf et al. includes 8mer (i.e. octamer) oligonucleotides which would necessarily hybridize wholly or in part to SEQ ID No. 1 and SEQ ID No. 4 under the claimed conditions.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2-6, 8-11, 17, 18, 20 and 24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a New Matter rejection.**

37 CFR 1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application".

MPEP §2163.06 notes:

If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981).

MPEP §2163.02 teaches that:

Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application.

MPEP §2163.06 further notes:

When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure. (Emphasis added).

The instant claims have been amended during prosecution to include the new limitations: "more than 8 nucleotides", "under conventional stringent hybridization conditions", and "more than 8 and up to 25 nucleotides" (e.g., See claims 2, 5, 20).

It is noted that Applicants have not indicated where in the specification they believe support for the new limitations can be found. Applicants are asked to identify by specific page and line number where support for the indicate limitations can be found.

Looking to the specification for support, the Examiner has found support for only for oligonucleotides that are "at least 6, preferably 8 to 25 nucleotides" (see p. 3, paragraph [0008]), and "the term 'hybridized' relates to the procedures known the art under conventional, in particular also under highly stringent hybridization conditions" (see p. 3, paragraph [0009]). However, this disclosure is not proper basis for the claimed limitations as the specification does

not specifically disclose "said partial sequence comprising more than 8 nucleotides", "under conventional stringent hybridization conditions", and "more than 8 and up to 25 nucleotides". Therefore, the new limitations are considered new matter.

To the extent that the claimed compositions and/or methods are not described in the instant disclosure, claims 2-6, 8-11, 17, 18, 20 and 24 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since a disclosure cannot teach one to make or use something that has not been described.

Response to Arguments

Applicant's arguments filed 9/20/05 have been fully considered but they are not persuasive.

With respect to the rejection of claims under 35 USC § 112, 1st paragraph (written description) Applicants argue that they have fully identified and characterized the protein named pKe#122, and indicate that the specification has contemplated vectors expressing pKe#122 and fusion proteins and variants thereof. Applicants contend that one of ordinary skill in the art, based on the teachings by Applicants, can select sequences that are 8 or more nucleotides and which hybridize to the pKe#122 sequences under conventional stringent conditions and that the sequences can be selected or discarded based on whether the sequences have the same functions as pKe#122.

These arguments are not persuasive. The courts have specifically stated that the skilled artisan cannot envision the *detailed chemical structure* of an encompassed polypeptide until the structure is disclosed, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. In the instant case, SEQ ID NO: 1 and SEQ ID NO: 4 have been disclosed as encoding polypeptides which have identical function (pKe#122 function). However, the specification does not disclose any sequence variants of SEQ ID NO: 1 or 4 that have identical function. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factors present in the claims are that the nucleotide sequence has a sequence of SEQ ID NO: 1 or 4 (i.e., any portion of SEQ ID NO: 1 or 4), and a requirement that the encoded polypeptide is functionally identical to pKe#122. ***There is no identification of any particular portion of the structure that must be conserved in order***

to conserve the required function(s). Clearly, such does not constitute disclosure of a representative number of examples of, nor adequate written description for, the claimed genus.

Therefore, Applicants arguments are not persuasive.

With respect to the rejection of claims under 35 USC § 112, 1st paragraph (enablement) Applicants argue that claim 18 has been amended to overcome the rejection and also assert that the specification has provided a proper description of the nucleic acids encompassed by the claims and that the specification has provided an enabling disclosure for a method of treatment using antisense oligonucleotides in vivo.

Applicants' arguments are not persuasive. With respect to the amendment, it is not clear how the amendment would overcome the instant rejection and applicants have not stated why the amendment would overcome the rejection. Therefore, the amendment to claim 18 does not overcome the instant rejection. With respect to the argument that the specification has provided a proper description of the nucleotides of the claims, it is respectfully pointed out that the instant claims encompass sense and antisense oligonucleotides for any nucleic acid that comprises "a nucleotide sequence" (i.e., any fragment) of SEQ ID NO: 1 or 4 wherein the nucleic acid encodes a protein that is functionally identical to pKe#122. However, as indicated above, the specification does not provide the proper description of the nucleic acids that encode a protein that is functionally identical to pKe#122. Therefore, the specification surely does not provide a proper description of the sense and antisense oligonucleotides that hybridize to the nucleic acids which are different from SEQ ID NO: 1 and 4 and which encode polypeptides that are functionally identical to pKe#122.

With respect to Applicants arguments that the specification provides a working example which demonstrates that the antisense oligonucleotides are effective for differentiating keratinocytes and that the specification has appropriate conditions for administering the oligonucleotides, it is respectfully pointed out that the specification has only disclosed a working example which demonstrates that specific antisense oligonucleotides were able to effectively differentiate keratinocytes in vitro. There are no examples which indicate that the methods would be effective in vivo, which is the only embodiment encompassed by the claim (i.e., the claim does not encompass an in vitro method).

With respect to Applicants contention, "The Examiner's assertion that pKe#122 is not involved in 'dermatological disorder' is in correct...", it is respectfully pointed out that the Examiner was only indicating that the *prior art* did not recognize that pKe#122 was involved in dermatological disorder. The specification does provide evidence to support the notion that that pKe#122 is involved in dermatological disorder. The fact that the prior art does not recognize pKe#122 as being involved in dermatological disorder is only indicated as an acknowledgment of the state of the prior art.

With respect to Applicants argument that page 8 of the specification discloses methods for treating epidermal diseases and that no working examples are required, it is acknowledged that the specification contemplates using antisense oligonucleotides for treating epidermal disease. Furthermore, it is acknowledged that no working examples are necessarily required -- provided that one of skill in the art could make and/or use that claimed invention based on the disclosure of the specification without having to perform an undue amount of additional experimentation. However, here, one of skill in the art would be required to perform additional

experimentation to be able use the claimed method to treat a disease *in vivo*. The Examiner has made this conclusion based on the teachings of the art relevant to antisense therapeutic methods, specifically Probst et al., and Harris et al. (see above). Applicants have not rebutted that teachings of Probst et al. and Harris et al., which clearly indicate that methods of using antisense oligonucleotides for in vivo treatments is unpredictable. Therefore, Applicants arguments are not persuasive.

With respect to the rejection of claim under 35 USC 102, Applicants argue that the claims have been amended such that the hexanucleotides taught by Boehringer are not encompassed by the claims.

In response, it is respectfully pointed out that the instant claims encompass any nucleotide sequence that hybridizes to at least about 8 nucleotides under conventional stringent conditions. A hexamer is a oligonucleotide that is 5 nucleotides in length. Boehringer teaches a composition comprising every possible hexamer. As such Boehringer teaches hexamers that are 100% identical to each 6 nucleotide segment of the nucleic acids encoding pKe#122. A 6mer that is 100% identical to 6 nucleotides of SEQ ID NO: 1 or 4 would certainly hybridize to a segment of the target sequence that is at least about 8 nucleotides in length under stringent conditions. Therefore, Applicants arguments are not persuasive.

With respect to the rejection of claim under 35 USC 102, Applicants argue that Mierendorf does not teach each and every element of the claims, it is respectfully pointed out that Applicants do not clearly indicate which limitations Mierendorf does not explicitly teach.

Furthermore, Mierendorf does teach appear to teach each and every limitation, as indicated above. As such, Applicants arguments are not persuasive.

With respect to the rejection of claims under 35 USC 112, 1st paragraph (new matter) Applicants assert that the specification does provide support for the indicated subject matter. Applicants arguments have been fully considered, as well as the portions of the specification which have been cited by Applicants; however, nowhere in any of the indicated passages does the specification explicitly, implicitly or inherently contemplate the new limitations "more than 8 nucleotides", "under conventional stringent hybridization conditions", and "more than 8 and up to 25 nucleotides". Therefore, Applicants arguments are not persuasive.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon Eric Angell whose telephone number is 571-272-0756. The examiner can normally be reached on Mon-Fri, with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

J.E. Angell, Ph.D.
Art unit 1635